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Migraine and plant antioxidant: Review article

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***Abstract*— The pathophysiology of migraine has been the subject of many works, the precise molecular mechanism regarding the disturbances that underlie migraine remains unknown. Additionally, it was found that oxidative stress contributes significantly to migraine development. For many years, the idea that migraine sufferers experience oxidative stress was addressed. In the last few years nutraceutics, includings antioxidants, have received a lot of attention among the substances which may be utilized to cure migraines. Antioxidants that are supplied with the food prevent the oxidative stress through suppressing the propagation, initiation, and actual oxidative chain reaction. The agents now being utilized to prevent migraines do in fact have a certain antioxidative activity. Antioxidants that have been addressed in this research are growing more regularly utilized through the migraine sufferers not just because of low or even lack of side effects, yet as well due to their efficiency (shortening of an episode duration or reduced frequency of migraine episodes).**

***Keywords*— migraine, antioxidants, oxidative stress, plant antioxidant.**

I. INTRODUCTION

Migraine as one of the complex multifactorial neurovascular brain conditions affecting information processing in the brain and causes attacks of recurrent, unilateral hemicranial pain [1]. According to estimates, migraine affects 12% to 16% of population, and it happens in women more than males (3:1), [2]. It was expected to be 50% in women and 20% in men in the first 10 years of the twenty-first century [3]. A unilateral pulsating/throbbing headache that lasts from 4 to 72 hours, generally accompanied by photo- and phonosensitivity, is the hallmark of episodic form of migraine [4]. A chronic migraine, which is a sporadic migraine complication, affects about 2% of the world's population [2]. Migraine with aura is a condition which affects about 30% of the patients with a confirmed migraine [5]. A migraine aura normally lasts for less than one hour. Then individuals get migraine headaches (less frequently tension headaches) after the aura [6]. Clinical features

regarding the migraine aura include, brief sensory and visual disturbances (bilateral or unilateral), along with motor symptoms brought on by recurrent brain dysfunction. The most frequently reported disturbances are visual [7]. When migraine attacks with aura medications like lamotrigine that prevent migraine attacks are typically introduced. Migrainous stroke, or an episode of cerebral ischemia with neurological impairments, could be exacerbated by aura [8].

Cortical spreading depression (CSD), a slow depolarization wave which spreads slowly across the cortex, is related to migraine aura' pathophysiology. Some researchers claimed that CSD is involves in the headaches' [9]. As previously mentioned, migraine is one of the brain disorders linked to changes in brain homeostasis that, stimulates regarding the nociceptors in cerebral vessels, activation of the trigeminovascular system, and increases the transmission of the signal in the brain. Therefore, additional signal transmission causes stimulation of certain brain regions that are in charge of migraine clinical manifestations. Yet, the pathophysiological mechanisms underlying the migraine are still not fully uncovered. Cortical hyperreactivity, where the brain has a higher sensitivity to the stimuli, is linked to the migraine' occurrence. Most possibly, it is related to a diminished ability for controlling interactions between the neurons (via inhibition) or with the pre-activation through brain stem or thalamus [5]. The afferent trigeminal ganglion fibers that innervate the meninges are thought to be activated in the migraine with aura, which has been thought to be the cause of cat scratch disease (CSD). Substance P, neurokinin A, could subsequently be released due to the activation described above[10] . The clinical manifestation regarding migraine is brought on by the release of aforementioned cytokines, which then causes endothelium and platelet activations, an increase in NO production, and vasodilation [10]. Glutamic and aspartic acids, along with GABA receptors, are thought to play a part in migraine's etiopathogenesis [11].

Phosphorus magnetic resonance spectroscopy (31 P-MRS) is a head examination of migraine sufferers it was used also revealed impaired oxygen metabolism and brain energy [11]. Also, this was supported by Gross et al., [12] who found that factors which often cause headache, such as physical exertion, fasting, sleep deprivation or excess sleep,

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photosensitivity or intense aromas, might have indirect or direct impact on mitochondrial activity and energy metabolism. As a result, these factors might cause oxidative stress and brain hypometabolism, which in turn might cause some pain [12].

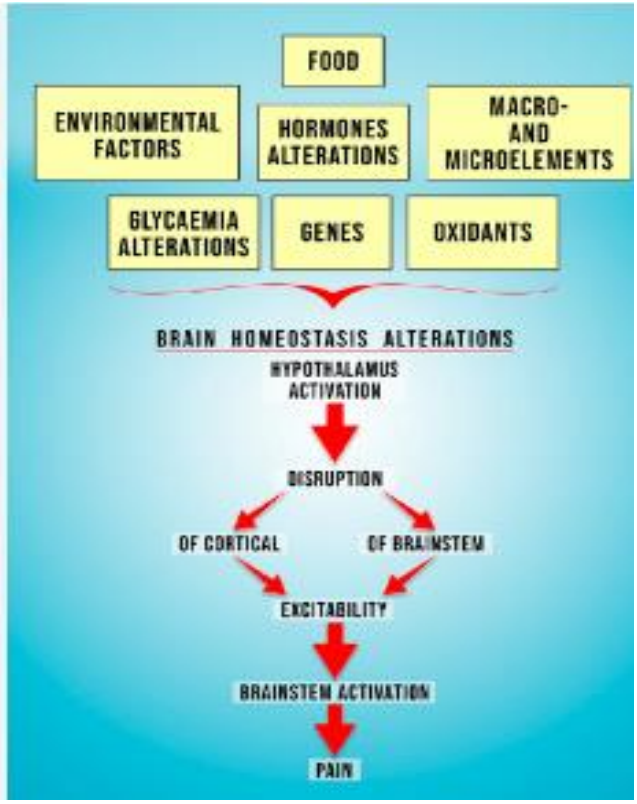

Fig 1. Neurobiological processes that lead to the migraine pains [13]

Migraine can be defined as "a recurring syndrome of headaches, which is coupled with various neurologic dysfunction symptoms in variable admixtures" or "an episodic headache linked with particular traits, like sensitivity to the light, movements and sound" [14]. Resistant migraines, defined as those that have "failed at least 3 migraine preventative classes and suffer from a minimum of 8 debilitating headache days each month for at least 3 successive months without improvements," and refractory migraines, defined as the ones that "have failed all available preventatives and suffer from a minimum of 8 debilitating headache days each month for a minimum of 6 successive months," are two categories for migraines [15]. Moreover, other syndromes with varying clinical manifestations, prevalence, and durations, including abdominal migraines, somnambulism, cyclic vomiting, benign paroxysmal vertigo, confusional migraine, and benign paroxysmal torticollis, could be connected to migraines [16].

Transient neurological symptoms (such as migraine aura), premonitory phase, a postdrome phase, and an intense headache attack are some of the phases of the cyclic disorder known as migraine [17]. Additionally, migraine is one of the burdensome diseases that affects a person's ability to work, engage in academic and social activities, along with their families and personal relations [18]. In the world, migraine accounted for 16.30% [95% uncertainty interval (UI): 11.7-20.8] of attributable disability-adjusted life-years (DALY) lost because of neurological disorders in the year 2016. Global age-standardized prevalence of the migraines grew by 1.70% (0.70–2.80) from 1990 to 2019, and in the

year of 2019 there were 1.1 billion (0.98–1.30) prevalent cases and 525.50 (78.80–1,194) years lived with disability (YLDs) per 100000 population [19]. In the US, migraine patients' financial burden has been considerably higher than that of non-migraine patients ($11,010 vs. $4,436; $p < 0.01$) [20].

Numerous factors were detected depending on many hypothesized migraine mechanisms [21], including head injury, advanced age, excessive medication or caffeine use, pain syndrome, lower socioeconomic status, sleep issues, stress, obesity, and pro-thrombotic or pro-inflammatory states [22] Along with the factors already listed, a number of other risk factors for chronic migraine, a migraine sub-type, were proposed. They include inadequate treatment for acute migraine and excessive pharmaceutical use [22]. Additional risk factors include lifestyle (such as weight gain, caffeine misuse, and sleep disorders) and demographic (such as race and sex) factors [23].

Even though previous works have suggested risk factors regarding chronification or migraine progression [22], there were no latest works on the risk factors related to migraines. Consequently, in the present study we extensively analyze the latest evidence on migraine risk factors, along with outlining the migraine history.

II. DISTINCTION BETWEEN MIGRAINE AND NORMAL HEADACHES

A headache can be defined as a pain in the head which comes and goes at random times, yet it is not a disease. The primary difference between the pain of a typical headache and the pain of a migraine sufferer is that, as opposed to dull pain of a tension headache, 85% of the migraine sufferers report constant pulsating, throbbing, or pounding pain that is felt with every heart-beat and feels like a knife is being repeatedly stabbed into the head. As a result, it was once believed that migraines cause by the brain's vasodilatation blood vessels pressing and expanding on pain-sensitive structures. However, experts are still unsure of the exact cause of migraines. Although migraines inherited in families, it is unclear why certain family members only get migraines. Even though any severe headache is referred to as a "migraine," a migraine headache occurs due to particular physiologic changes taking place in the brain [24].

III. TYPES OF HEADACHES

Individuals who have a family history of migraine will have them frequently, and the discomfort will last throughout the neck region and head. Headache can be specified as a symptom brought on by a number of illnesses that are activated in the neck and head. Because there are no pain receptors in brain tissue, it is non-sensitive to pain. Around the neck and head, discomfort is brought on by sensitive muscles, arteries, nerves, subcutaneous tissue, veins, ears, eyes, sinuses, etc. Depending on the origin and cause, there are two sorts of headaches: 1. A primary headache. 2. A secondary headache [25].

A. Primary headache:

Those headaches are the most typical one. This group includes headaches such as tension headaches, migraine, hemicrania continua, and cluster headaches. The most typical headache type is one that caused by tension in the neck and head muscles. These primary headaches also include pulsing pain in the head, discomfort in the brows, nausea, a band-like tightness in the upper region of the neck, and occasionally vomiting. The pain lasts for three hours to three days. According to outdated views, migraine aura resulted by intracranial vasoconstriction. According to a new idea, migraines are caused by the cerebral cortex's occipital cortex's neuronal hyperexcitability [25].

B. Secondary headache:

Some neck and head issues might result in headaches. A few of them don't pose a threat. Subarachnoid hemorrhage, which is brought on by a stroke where blood accumulates surrounding the brain, is what causes thunder clap headaches. Meningitis causes a stiff neck and headache in addition to a fever. Increased intracranial pressure brought on by a brain tumor, idiopathic intracranial hypertension or cerebral venous sinus thrombosis causes headaches that are made worse by strain and positional changes. Giant cell arthritis, which results in an inflamed blood vessel wall that obstructs blood flow, causes headaches with visual disturbances. Angle closure glaucoma can cause nausea, headache, dizziness, and a feeling of weakness in the muscles. Carbon monoxide poisoning can often result in nausea, headache, and vomiting[25].

IV. OXIDATIVE STRESS ROLE IN MIGRAINE PATHOPHYSIOLOGY

Although migraine pathophysiology has been extensively studied, the precise molecular basis of the abnormalities that underlie migraine remain unknown [25]. The hypothesized theories place a lot of emphasis on oxidative stress [26], which is defined as disruptions in the ROS production-degradation balance. [27]. As a result, several disorders, including atherosclerosis, decreased kidney function, and ischemic stroke, are caused by this process [28]. In the past few years, the migrain has also been linked to the onset of neurodegenerative and neuroinflammatory illnesses of central nervous system, like Alzheimer's disease, multiple sclerosis, and Parkinson's disease [27]. For many years, the idea that migraine sufferers experience oxidative stress was addressed.

In the individuals who have migraine with aura during times without attacks, Tozzi-Ciancarelli et al., [29] showed an increase in the concentration of the substances interacting with the thiobarbituric acid [29]. A research on the indicators regarding cell redox status in migraine sufferers was undertaken a few years later by Alp et al., [30] and revealed differences in total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI). In individuals with migraine with no aura, recorded TAS values were lower, however TOS values have been significantly higher in comparison with the controls [30]. Geyik et al. [31] looked at the characteristics of oxidative stress as well as oxidative stress-dependent DNA damages that are assessed by 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels in migraine patients (without as well as with aura, divided to corresponding sub-groups) [31]. The findings demonstrated that there were no variations in the TAS, TOS, and OSI values between control group (healthy individuals who do not have migraines) and the study group. Also, there have been no variations in TOS, TAS, and OSI values between the groups of individuals who had migraines without and with aura [31]. Yet, a considerably greater plasma concentration of 8-hydroxyguanosine (8OHdG) was seen in migraine patients in comparison with control, along with the group of the patients who had migraines with no aura compared to the group who had migraines with aura [31].

Yigit etal. [32] demonstrated there was damage to the plasma lymphocytes, highly impacted by oxidative stress, in their investigation on the patients who have diagnosed migraines. Urotensin receptor (UTS2R), a peptide that is found in blood and heart vessels, was measured in the authors' serum samples. The aforementioned peptide has potent vasoconstrictive characteristics, and patients with migraine without aura were shown to have higher concentrations of it [32]. Identification of plasma MDA concentration, TAS, TOS, and OSI levels, along with CAT activities, were added to the research [32]. The findings of this investigation revealed that migraine sufferers had considerably higher OSI and TOS values, higher levels of lymphocyte DNA damage, and higher MDA concentrations than controls. Yet, it was discovered that the study group's levels of UTS2R, TAS, or CAT activity was lower than those of control group [32].

The latest research have shown that in the migraine patients, elevated oxidative stress and reduced antioxidant levels might result in vascular inflammation [33]. It has been reported preciously a lot that there is a connection between neurogenic inflammation and migraine [34]. In spite of the fact that the oxidative stress is thought to have a significant impact on the migraine's pathogenesis, there have not many works done on blood markers regarding antioxidant status in migraine. As endogenous ROS scavengers, total bilirubin (TBIL), serum albumin (ALB), uric acid (UA), and creatinine (CRE) represent prominent non-enzymatic antioxidants in the human plasma, according to more recent research [35]. (figure 2). It is unclear if such markers could demonstrate that oxidative stress is a factor in the pathogenesis of the migraines. It could be feasible to contribute to reducing migraine headache attacks' frequency and slowing the progression by early detection of the potential effects of the oxidative stress on the migraine patients.

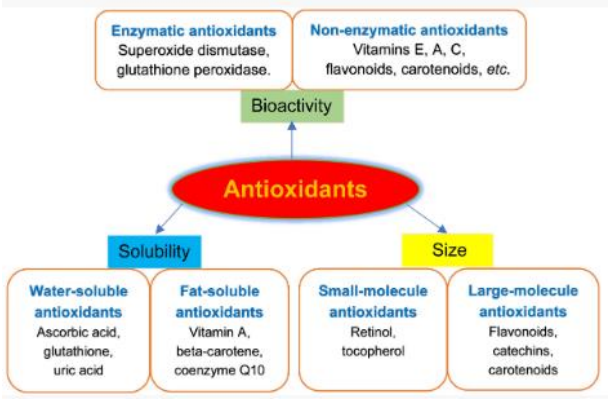

Fig. 2: Oxidative stress affects different systems and antioxidant defenses including natural bioactive molecules [36].

V. ROLE OF HOMOCYSTEINE IN MIGRANE

A higher homocysteine (Hcy) serum level might be diagnosed seen in migraine sufferers who frequently have them. One of the possibilities that having higher Hcy in blood are the temporary thrombosis or vasodilation of cerebral blood vessels that are brought on by the Hcy [37]. Moreover, enhanced prothrombin activation or von Willebrand factor, the cause of hypercoagulable state, also can be resulted from through the increase having higher Hcy serum levels, are the cause of hypercoagulable state [38]. The higher risks for cardiovascular events and stroke in such be explained by the association between hypercoagulation and Hcy [39]. Moreover, the formation of the superoxide anions by Hcy could contribute to migraine development (figure 3) by causing oxidative damages to vascular endothelium [39].

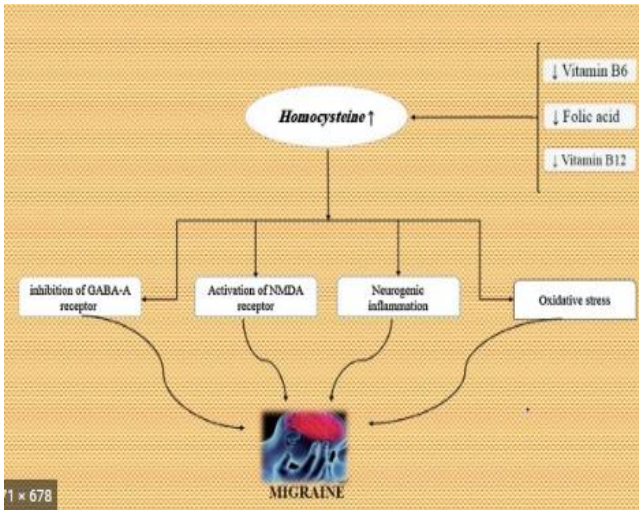

Fig. 3: The role of Hcy in migraine. [40]

VI. MIGRAINE AND PLANT ANTIOXIDANTS

Different processes have been involved in migraine pathogenesis , making it a multifactorial condition [39]. As result, no single medication could be helpful in all migraine sufferers. Triptans were suggested for acute treatment for many decades [41]. Preventive care is necessary for patients who experience frequent migraine attacks that have a negative impact on their life. Patients with the occasional migraine attacks typically require rescue medications in order to relieve the pain [41]. It is still necessary to find substances with a better tolerance and a milder effect, causing fewer adverse effects [42], because of the side effects associated with the use of usual prophylactic medications (antiepileptic medications, calcium channel inhibitors) or abortive therapy [41]. Migraines disease is more common youth, therefore is very important to pay attention to it [43].

The Nutraceutics have drawn a lot of attention in recent years among the substances which might be utilized for treating migraines [44] Vitamins (like riboflavin) and dietary supplements like coenzyme Q10 and alpha lipoic acid are among the items in this category [44]. By preventing the initiation, propagation, and oxidative chain reaction itself, antioxidants present in diet reduce oxidative stress. Additional ways that antioxidants from food work include scavenging free radicals, quenching molecular oxygen, and serving as reductants in the oxidative processes [45]. Current study on the migraine pathogenesis pathways has advanced understanding of potential therapy options. According to current knowledge, the complexity regarding migraine's pathogenesis is thought to be affected by a variety of the environmental factors, including epigenetic and genetic factors [46]. Also, as was already noted, is oxidative stress is considered as a key factor in pathogenesis of migraines. Antioxidants can be used to modulate the effects of oxidative stress [46]. The agents have been used so far for preventing migraines exhibited certain antioxidant activity [46].

Natural antioxidants can also be obtained through food sources, such as vegetables, flowers from edible plants, fruits, and spices that are made from the plants, in addition to supplements [47]. Polyphenols (anthocyanins, phenolic acid, flavonoids, phenolic acid and lignans), carotenoids (carotenes & xantophylls), and vitamin E and C are the most prevalent plant antioxidants [47]. The primary plant antioxidants are polyphenols, which have a variety of functional, structural, and biological properties [48]. The shikimic acid pathway allows tyrosine or phenylalanine to be converted into phenolic compounds. They could range from straightforward substances to conjugated complex ones. Those compounds range in molecular weight from 500 to 4000 Da, and the phenolic compounds contain over 12 phenolic hydroxyl groups [49]. They could be divided into lignans, flavonoids, stilbenes, and phenolic acids [50]. They can be present in plant-based products like tea, wine, and vegetable oils as well as in foods like grains, fruits, berries, and seeds [51]. Figure (4) depicts a summary regarding the phenolic acids' breakdown.

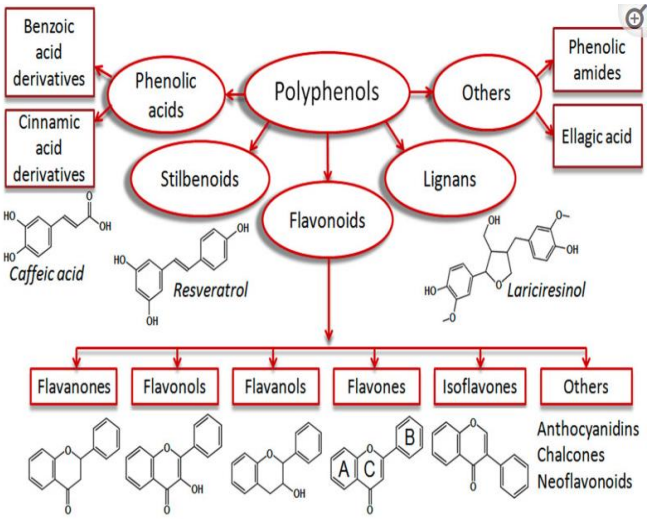

Fig. 4: Plant phenolic compound breakdown [51].

A. Garlic

More than one billion individuals all over the world suffer from migraines, it consdiers one of the most prevalent and debilitating neurovascular disorders [52]. According to accepted migraine theory, the pain related to migraines is partly caused by vasodilatation of major cerebral arteries. We present a different theory for the pathophysiology regarding vascular migraines, according to which persistent cerebral microvascular constriction is caused by stress-induced elevated sympathetic tone [52]. After nociceptors are activated as a result of decreased central parenchymal blood supply, headaches may start to develop. Our hypothesis is that the prevention or the lessening of the chronic micro-vascular constriction will decrease the severity or frequency of the headaches that are caused by the vascular system.

Present migraine medications have a number of drawbacks, such as high costs, invasive subcutaneous administration, regulatory restrictions, and medication overuse which paradoxically causes headache [53]. Many of these medications are also vasoconstrictive, which is a contraindication for the patients who have cardiovascular complications [54]. Thus, it is vital to investigate benign vasodilating alternatives for preventing and treating individuals with vascular-induced headaches. Aged garlic extract (AGE) and L-arginine (2-amino-5-guanidinopentanoic acid, arginine) are two oral nutraceuticals that were utilized to reduce many CVD risk factors through the vasodilatory mechanisms [55]. Yet, neither has been researched as a prophylactic treatment for episodic chronic migraines. In short, AGE and L-arginine are likely to be effective in the reduction of the migraine frequency/severity, which is caused by cerebral microvascular constriction via improved bio-synthesis of the endothelial nitric oxide (L-arginine) or increasing systemic vasodilatory prostaglandins (AGE), among other antioxidant and anti-inflammatory characteristics. The safety profile of both of such nutraceuticals was extensively studied and was well-tolerated in cardiovascular indication contexts with few side effects, which is a considerable benefit over current standard migraine medication therapies.

Fig. 5: An illustration of general medicinal applications of allicin [58].

B. Curcumin

ROS generation is dramatically increased when solar ultraviolet radiation (UVR) is exposed to human skin, tipping the natural balance in favor of an oxidative state and causing oxidative stress [59]. The most severe result of photodamage is skin cancer, which is caused by oxidative stress. Other undesirable and harmful skin illnesses are scaling, aging, mottled pigment, dryness, and scaling [60]. A number of photochemical processes, including modifications to the oxidation of nucleic acids, DNA sequence, and functional changes to lipids and proteins, are the root cause of such numerous negative impacts. Hence, controlling ROS levels is essential for maintaining healthy skin homeostasis [61]. Because of its various phenolic groups that have positive effects on a variety of human illnesses and its low toxicity, curcumin has recently emerged as an attractive choice among other natural-derived components [62]. Turmeric rhizomes, which are also referred to as the Curcuma longa, contain a naturally occurring lipophilic polyphenol called curcumin (Cur) that had gained recognition as bioactive substance with strong anti-oxidant capabilities. It is difficult to directly incorporate Cur into various supplement products and pharmaceutical formulations because of its high chemical instability, low oral bioavailability, and poor water-solubility, even though however it could have potential health benefits in the case when ingested orally at adequately high levels [63]. Researchers have documented a number of methods for increasing curcumin bioavailability, including creation of the liposomal curcumin [64], nanocurcumin [62], curcumin-phospholipid complex [64], and metal chelation [65]. The production of the inclusion complexes with the cyclodextrins, specifically cyclic oligosaccharides generated by the non-reducing chiral glucose-building blocks that are coupled with a ring structure, could also be used to solve solubility problems [66]. These methods deliver Cur in its active state while simultaneously enhancing Cur's solubility and stability. Among these carriers, cyclic bucket-shaped oligosaccharide β-cyclodextrin (β-CD) is frequently utilized. It is a semi-natural substance that improves drug delivery through biological membranes and has incredibly low toxicity [67]. Scientists have lately begun to think more and more about using curcumin to treat migraines. Bulboaca et al.,[68] have examined the effectiveness of sumatriptan (ST) utilized alone versus when combined with the curcumin.

A nitroglycerine-induced migraine in a rat model has been used for the investigation. Because of the decreased gastrointestinal absorption of curcumin, it was given in an intravenous manner as: i) an alcoholic solution (i.e. diluted in the saline), and ii) liposomes . The antioxidative effects of curcumin were documented by the authors for every dose and application form (i.e. solution/liposomes), including a drop in MDA concentration, a reduction in RNS production, a reduction in TOS, and a TAS increase. Curcumin's antioxidative abilities, on the other hand, were found to be more potent when it was given in the form of liposomes. The capability of curcumin for scavenging peroxyl or hydroxyl radicals, direct interaction with the peroxide radical anion, and the inhibition of activity of the κB nuclear transcription factors (NF-κBs), involved in pro-inflammatory factors' transcription, are all credited by the authors as explanations for the observed results [68]. The same researchers compared the effects of the curcumin and naproxen solution on pain perceptions and oxidative stress parameters in a separate investigation employing a rat model of migraine (which is caused as well by the nitroglycerine) [69]. Liposomal curcumin administration decreased MDA levels, decreased nitrogen oxide (NO) generation, reduced TOS values, and reduced nociception. In comparison to naproxen used alone, the antioxidative mechanisms were observed to be enhanced in the case when naproxen and curcumin have been administered (thiol rise and increased total antioxidant capacity, TAC). Yet, the authors claimed that patients who received curcumin in the form of liposomes saw a stronger antioxidative impact [69]. Yet another research [68] supported the beneficial antioxidative and analgesic curcumin effects in comparison to the use of indomethacin and propranolol. There are also some studies have been done on to see the studies on potential curcumin in treatment of migraines. TNF-α is thought to have an impact on the pathogenesis of migraines. TNF-α causes neuronal hyperexcitability, nociceptors to be stimulated, and prostanoid synthesis to take place, all of which contribute to the development of migraine symptoms and the beginning of neuroinflammation [70]. To determine synergistic impacts of the curcumin and 3 acids on TNF-α gene expression,

Abdolahi et al., [70] studied a group of patients who have sporadic/episodic migraines. Individuals who have received both medications had lower plasma levels of TNF-α mRNA, which indicates that TNF-α expression had decreased [70]. Patients with sporadic migraines participated in the study on anti-oxidative effects of the nano-curcumin combined with the coenzyme Q-10 (figure 5). According to the findings of this investigation, combining curcumin and coenzyme Q10 supplementation can reduce length, frequency, and intensity of the migraine attacks [71].

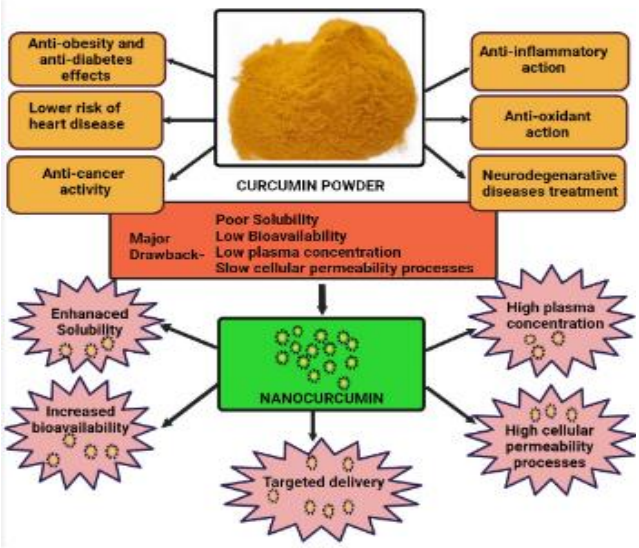

Fig. 6: The multifaceted role of nanocurcumin in treatment of neurogenerative diseases. [72].

C. Coenzyme Q10

Ubiquinone, which is often referred to as coenzyme Q10, is a naturally occurring lipid compound that is lipid soluble and has 10 isoprenoid units in its molecule [73]. It has antioxidative capabilities and shields cells from excessive ROS generation, which stops excessive nucleic acid oxidation or lipid membrane peroxidation (figure 7). Coenzyme Q10 has antioxidative and anti-inflammatory effects in addition to be a cofactor in the synthesis of pyrimidine, which is a step involved in RNA repair and DNA replication [73]. Moreover, it influences gene expression and the physiochemical characteristics of cell membranes [74]. In respiratory chain, where it serves as electron carrier, coenzyme Q10 is an important component (Hargreaves and Mantle, 2019). It is regarded as dietary supplement in various neurological illnesses, like the amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Parkinson's disease and Friedreich's ataxia, because of its potential advantegs [73]. Given that one theory on migraine pathogenesis states that mitochondrial metabolism is disturbed, coenzyme Q-10 is utilized and examined for potential applications in the treatment of migraines. Coenzyme Q-10 is a factor which affects maintaining mitochondrial metabolism [75]. Antiepileptic drugs (valproic acid and topiramate), blockers (propranolol), and anti-depressants (amitriptyline) are recommended as the first-line therapeutic drugs for migraine prevention by the experts (for example, American Academy of Neurology). Because they have significantly less or even no adverse effects compared to the above mentioned first-line treatment medications, nutritional supplements like coenzyme Q10 can be alternative medication [76]. In fact, one of the most widely utilized remedies for preventing migraines is coenzyme Q10 [77]. The fact that coenzyme Q10 causes a drop in the calcitonin gene-related peptide (CGRP) that establishes the level of the CGRP as target of the preventative treatments for the migraines, has recently drawn increased attention [78].

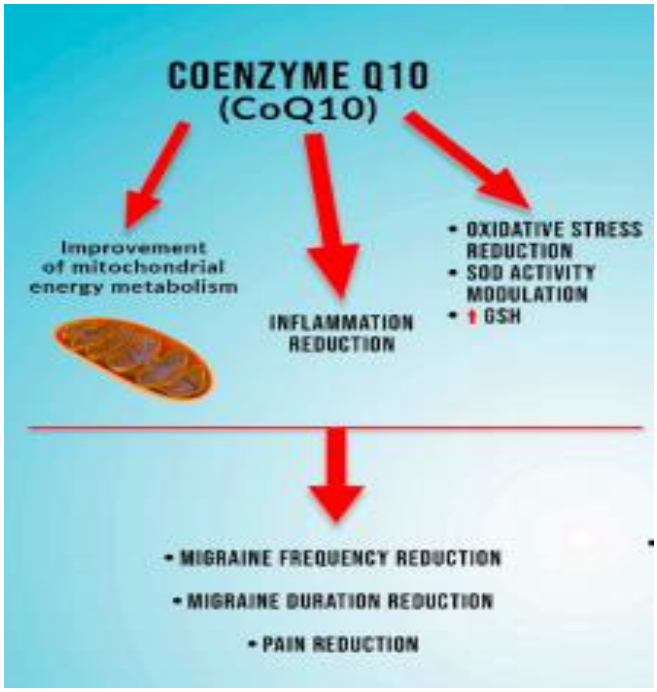

Fig. 7: Effect of Coenzyme Q10 on red - ox status parameters in patients who have migraine. [13].

D. Ginkgo biloba herb

Ginkgolide B is a natural component of Ginkgo biloba (GB) leaf extract (figure 7). It is one of the most well-known and frequently utilized items with a plant origin. Its long-term and regular prescription is an essential part of the secondary and primary prevention of a variety of disorders, including anxiety, depression, headaches, and memory deficiencies [79]. The literature on the topic emphasizes the neuro-protective qualities of GB leaf extract, although the precise mechanism regarding its neuroprotective activity needs more research [79]. It was demonstrated that the GB leaf extract had helped to prevent hippocampus neuronal death, a result of the TGA, because of its anti-inflammatory and antioxidative properties [80]. Terpene lactones and flavonoids are the primary biologically active components of GB leaf extract [12]. Certain authors believe quercetin, not ginkgolide B, is responsible for the antioxidative activity [82]. Nonetheless, ginkgolide B is the most nutraceutical agent that frequently described as being utilized to alleviate migraines [83]. The research on the topic indicates its antioxidative characteristics [84], even if its primary method of action in migraine has been thought to be regulation of platelet-activating factor (PAF) receptor antagonism and brain glutamatergic transmission [85]. Considering alterations in redox status during migraine, this seems crucial. Ginkgolide B is one of the primary components of the Ginkgo biloba leaf extract that has favorable benefits on memory, along with ginkgolides A, C, and terpenes [86]. In a 6-month, open-label, multicenter research, D'Andrea et al.

[80] found that the ginkgolide B was effective in the treatment of the migraineurs with aura who had at least one migraine episode per month. The study's participants were healthy people with no comorbidities, specifically no cerebral focal activation. The patients took the Migrasoll® formulation twice daily (60mg of the GB terpenes phytosome, 11mg of the CoQ10, 8.7mg of vitamin B2) for the next 4 months (the study period has been divided to two stages lasting 2 months each). According to 42.20% of the patients who had reported no more migraine attacks at the research's end and 5 patients who experienced no side effects from the prophylactic Migrasoll® treatment, the study group's patients had considerable decrease in frequency of migraine attacks. Adding supplements led to a reduction in the length of the aura during the entire trial period [81].

Fig. 8: Influence of GB leaf extract antioxidant on the red - ox status parameters in the patients who have migraine [13].

E. Feverfew (Tanacetum parthenium)

Feverfew (Tanacetum parthenium) is a well-known plant for preventing migraines [87]. Since ancient times, it was utilized for treating a variety of conditions, including migraine symptoms as well as pain from other sources, nausea, inflammation, and vomiting [88]. The potential use of feverfew in the treatment of headaches was reported since the 1970s [82]. The Asteraceae family includes Tanacetum parthenium L. (LNP23 TP), which is majorly dispersed throughout South America. It exhibits essential antioxidative characteristics and has a significant ability for inhibiting aldose reductase activity [88]. Sesquiterpene lactones which found in the leaves of feverfew (Tanacetum parthenium), with parthenolide being the primary biologically active component [88]. Other biologically active components found in feverfew include aromatic compounds (like camphor) and flavonoids (luteolin, apigenin) [88]. Wu et al., [84] demonstrated this [88]. Tanacetum parthenium, magnesium, and 5-hydroxytryptophan are all components of the Aurastop medication, which is utilized to treat migraine aura. The idea of a very early intervention and blocking the aura at this time was mentioned by [89]. Inhibiting the migraine aura may benefit both the migraine itself and its associated headache. Results, on the other hand, point in a different direction. Randomized double-blind placebo-controlled experiments by Ernst and Pittler had revealed that feverfew was ineffective in treating migraines [89]. The efficiency of feverfew in treating migraines in comparison with placebo was not confirmed by the authors based on the outcomes of randomized double-blind trials [89].

VII. CONCLUSION

Uncertain mechanisms underlie the pathogenesis of migraine, a multifactorial and complex brain condition. Because of the complexity of migraine pathogenesis, every patient responds differently to treatment (both acute and preventative). One of the mechanisms that are involved in migraine etiopathogenesis is thought to be oxidative stress, which is concidered as changes in the balance between ROS degradation and production. The investigations on nutraceuticals with antioxidant characteristics were summarized in the current study. The findings therein appear to support the potential use of antioxidant-rich nutraceuticals as an alternative to commonly prescribed migraine medications.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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